# PATENT SPECIFICATION

747,293

*Date of Application and filing Complete Specification March 15, 1954.*
*No. 7503/54.*
*Application made in United States of America on April 14, 1953.*
*Application made in United States of America on March 1, 1954.*
*Complete Specification Published April 4, 1956.*

Index at acceptance :—**Classes 2(3)**, AA(1C2A : 2A3) ; **and 81(1)**, B2(C : D : G : H : L : M : R : S).

COMPLETE SPECIFICATION

## Therapeutic Preparations containing Erythromycin Stearate

We, ABBOT LABORATORIES, (Manufacturers), a corporation organized and existing under the laws of the State of Illinois, with a principal place of business at 14th Street and Sheridan Road, North Chicago, Illinois, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the methed by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to an oral suspension having erythromycin activity and to a method for making it.

Erythromycin is an antibiotic which is produced by a strain of streptomyces erythreus which was isolated from a soil sample collected from the Philippine Islands. The antibiotic shows rather broad activity against bacteria and certain other micro-organisms. It is a crystalline antibiotic having a basic nature and is soluble to the extent of about 2 to 4 mg./ml. in water. It is soluble in a number of organic solvents. It has a melting point of about 130° C. to 135° C. and an optical rotation $(\alpha)^{25}D$ of about −78°. Considerable data on the indentification of the antibiotics is contained in Antibiotics and Chemotherapy, Vol. 2, No. 6, pg. 281, (June 1952).

It is well recognised in the art that an oral suspension having erythromycin activity would be a very desirable dosage form for this product. Oral suspensions are highly suitable for administration to children and to some adults. The principal difficulties in administering erythromycin orally arise from the fact that it has an extremely bitter taste and that it is destroyed or inhibited by acidic gastric secretions. The antibiotic is therefore unsuitable for administration orally in its basic form.

It is an object of this invention therefore to provide an oral dosage of erythromycin in the form of a suspension which is substantially free from a bitter taste and which will give adequate blood levels even when administered after meals when gastric acidity is highest. Another object of the invention is to provide a convenient oral dosage form of erythromycin as a suspension in which the erythromycin activity can be adjusted to provide a suitable dosage per unit volume.

In the accomplishment of the foregoing objects and in accordance with the practice of this invention there is now provided an oral suspension having erythromycin activity and having highly desirable therapeutic properties. The suspension comprises an aqueous suspending medium for the erythromycin, a finely divided solid erythromycin stearate, a buffer, and a suspending agent for suspending the erythromycin stearate salt is quite insoluble in aqueous media and has greatly reduced bitterness as compared to erythromycin base. When suspended in accordance with the practice of this invention in an aqueous suspending medium and in the presence of a buffer, the therapeutic composition provided in this manner is pleasing to the taste and provides high erythromycin blood levels even after meals.

While sodium citrate is the preferred buffer for use in this composition it is also intended that any buffer which is physiologically acceptable and which is capable of maintaining the *p*H of the suspension within the range of 7 to 10 may be employed in the composition. The *p*H of the suspension should not be allowed to exceed a value of 10 since at higher *p*H values erythromycin stearate is unstable. It is contemplated that we may use any physiologically acceptable acid neutralizing base or salt of a strong base and a weak acid. For example, we may use aluminium hydroxide, calcium hydroxide, sodium acetate, magnesium trisilicate, sodium phosphate, calcium carbonate, sodium bicarbonate and sodium carbonate. The term " physiologically acceptable " is used in order to distinguish the useful members from unacceptable bases and salts which are known to be toxic. In the pharmaceutical art the term " buffer " is commonly used to describe the physiologically acceptable acid neutralizing bases and salts even though it is not strictly accurate to refer to the bases as buffers. For instance, calcium carbonate and aluminium hydroxide are called " buffers " in the pharmaceutical art.

[*Price 3s. 0d.*]

Price 4s 6d

Price 5s. 0d.

An amount of buffer is added which will adjust the *p*H of the suspension to a value between 7 and 10, as illustrated in the Example. Naturally we may use any of the buffers alone or we may use a suitable combination of buffers. For instance, we may use aluminum hydroxide for its buffering effect and we may add sodium citrate both for its buffering effect and for its taste masking effect.

It has been conclusively shown by clinical tests in humans that the buffered erythromycin suspension referred to herein gives adequate erythromycin blood levels when administered either before or after meals. This result is significant in view of published data to the effect that erythromycin base does not give suitable blood levels when administered at a time when the gastric secretions are highly acidic (after meals).

The following example is presented in order to teach the details of the invention more clearly but without intending in any way to be a limitation on the invention. A suspension was compounded from the following ingredients:—

| | |
|---|---|
| Erythromycin stearate | 20000 mg. of activity |
| Methyl *p*-hydroxybenzoic acid ester (aseptoform M) | 1.0 gm. |
| Propyl *p*-hydroxybenzoic acid ester (aseptoform P) | 0.2 gm. |
| Sodium citrate | 100.0 gm. |
| Sodium carboxymethyl-cellulose | 3.0 gm. |
| Veegum (a complex colloidal magnesium aluminium silicate gel) | 10.0 gm. |
| Sodium lauryl sulfate | 1.0 gm. |
| Sucrose | 750.0 gm. |
| Bright orange dye | 0.02 gm. |
| Oil cassia U.S.P. | 1.2 cc. |
| Distilled water q.s. | 1000.0 cc. |

Since the potency of erythromycin stearate varies somewhat with a particular lot of erythromycin it is more desirable to express the quantity thereof in terms of the mg. of activity /1000 cc. of suspension. The average potency of erythromycin stearate is around 600 $\mu$/mg. but lots have been known to have somewhat lower and higher potencies. It is a simple matter to factor the erythromycin potency to determine the number of gm. of erythromycin stearate which will be required to provide 20,000 mg. of erythromycin activity. For example if the potency of a sample of erythromycin stearate is 600 units per milligram, 33.33 gm. of this sample will be required to give 20,000 mg. of activity.

The foregoing ingredients are compounded into an oral suspension by first heating 500 cc. of the water to the boiling point and dissolving the Aseptoforms therein. The solution is then divided into two-250 cc. portions.

To one part is added the carboxymethylcellulose and to the other part is added the sodium lauryl sulfate and the Veegum. The two portions are then combined and stirred until uniform. Thereafter the orange dye is dissolved in 5 cc. water and added slowly with stirring until uniformly distributed and the oil cassia is added in the same fashion. The sodium citrate and sucrose are then added and dissolved and the solution is evacuated to remove entrained air bubbles.

The previously prepared vehicle or suspending medium is gradually added to the erythromycin with stirring to form smooth uniform suspension. The entrapped air bubbles are removed by evacuation and the remainder of the water necessary to make 1000 cc. of suspension is added.

It will be apparent that the preservatives, the wetting agent, the sweetening agent, and the color and flavor are added in order to give the suspension a pharmaceutically acceptable appearance and taste. The amounts of these elements may be varied to meet any individual situation and taste. The sodium citrate is employed in order to protect the erythromycin from destruction by acidic gastric secretions. While the reason is not known the addition of sodium citrate also effectively masks and inhibits the bitter taste of the erythromycin stearate. The amount of suspending agent can be varied somewhat depending upon the number of gm. of erythromycin stearate required to provide the designated activity. Both carboxymethylcellulose and Veegum (a complex colloidal magnesium aluminum silicate gel forming agent) are suspending agents.

The erythromycin stearate is a reaction product of erythromycin with stearic acid and is found to have a solubility in water of about 0.13% or about 980 $\mu$/cc. One preparation of the salt is as follows:—

A solution of erythromycin base is prepared by dissolving about 15.0 gm. of the base in 80 ml. of methanol. To this solution 5.7 gm. of stearic acid is added and dissolved by heating the mixture to about 50° C. The solution is clarified by filtration and the filtrate is diluted with 160 ml. of water at 50° C. The solution is allowed to cool to room temperature (about 23° C.) where needle-like crystals of erythromycin stearate begin to separate. After standing for 2 to 3 hours in order to

allow complete crystallization the material is removed by filtration, washed with about 150 ml. of water and dried in a vacuum chamber. The product weighs 17.2 gm. and has a melting point of 80° C. to 82° C. The potency of the salt by microbiological assay vs. B. subtilis is found to be about 780$\mu$/m. The theoretical potency was calculated at 730 $\mu$/mg. The formula calculated from microanalytical analysis is $C_{57}H_{109}NO_{15}$.

What we claim is:—

1. A therapeutic composition suitable for oral administration comprising an aqueous suspending medium, a finely divided substantially water insoluble, solid erythromycin stearate, a buffer, and a suspending agent for suspending said erythromycin stearate in said liquid medium.

2. A therapeutic composition for oral administration having erythromycin activity comprising an aqueous suspending medium, finely divided, substantially water insoluble erythromycin stearate salt, sodium citrate, and a suspending agent for suspending said erythromycin stearate salt in said liquid medium.

3. A therapeutic composition for oral administration having erythromycin activity comprising per cc. of suspension, about 20 mg. of erythromycin activity in the form of erythromycin stearate, about 0.1 gm. sodium citrate, about 0.013 gm. of suspending agent, about 0.75 gm. sucrose and sufficient water to make up to 1 cc. of suspension.

4. The method of making an oral therapeutic suspension of erythromycin stearate which comprises mixing a suspending agent with an aqueous suspending medium, buffering said medium to a *p*H value between 7 and 10, and incorporating a finely divided, substantially water insoluble erythromycin stearate salt in said mixture.

5. The aqueous suspension of erythromycin stearate substantially as described and exemplified herein.

6. The novel method of preparing an aqueous suspension of erythromycin stearate substantially as described and exemplified herein.

Dated this 15th day of March, 1954.
PAGE, WHITE & FARRER,
Chartered Patent Agents,
27, Chancery Lane, London, W.C.2,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1956.
Published at the Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.